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Characterization of a Novel Nav1.5 Mutation in Brugada Syndrome

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Brugada syndrome (BrS) is an inherited channelopathy characterized by an increased risk for sudden cardiac death due to ventricular fibrillation. The major disease gene for BrS is SCN5A encoding the primary alpha-subunit of the cardiac NaV1.5 channel. Thus, exploring SCN5A mutations in patients with inherited arrhythmogenic syndromes is critical for understanding the pathogenesis of arrhythmias.

Recently, we identified a heterozygous NaV1.5 mutation, R893C, located in the S5-S6 loop of DII, in a male proband diagnosed with BrS. To investigate whether R893C is associated with BrS, we determined the biophysical properties of R893C using conventional patch-clamp combining with pharmacological tools.

We found that R893C is a loss-of-function mutation with slower activation kinetics of Na current and a significant rightward shift on the steady-state inactivation. R893C had no dominant negative effect on the WT channels. DTT might restore the normal function of R893C by reducing the cysteine bridges that may be responsible for the loss of conduction. We propose the observed phenotype of the proband is mostly due to the R893C mutation.

Our findings contributes to identify mutational hotspots in BrS that helps in understanding of arrhythmogenesis mechanisms. Moreover, our work may improve novel gene therapy and new therapeutic drug design targeting for SCN5A channelopathies.